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IN THE UNITED STATES PATENT & TRADEMARK OFFICE

IN RE APPLICATION OF: :

YUSUKE AMINO ET AL : EXAMINER: ZUCKER

SERIAL NO. : 10/091,500 :

FILED: MARCH 7, 2002 : GROUP ART UNIT: 1621

FOR: METHOD FOR PRODUCING ASPARTAME DERIVATIVE, METHOD FOR PURIFYING THE SAME, CRYSTALS THEREOF AND USES OF THE SAME

DECLARATION UNDER 37 C.F.R.§1.132

COMMISSIONER FOR PATENTS
ALEXANDRIA, VA 22313-1450

SIR:

Now comes Yusuke Amino, who deposes and states that:

1. I am an inventor of the above-identified application.

2. I am a graduate of the Faculty of Engineering of Kyoto University, and received my Ph. D. degree in the field of Organic Synthesis, in the year 1991.

3. I have been employed by Ajinomoto Co., Inc., for 21 years as research chemist in the field of Chemistry.

4. I understand the English language or, at least, that the contents of the Declaration were made clear to me prior to executing the same.

5. The following experiments and analysis were performed by me or under my direct supervision and control.

6. The Examiner asserts that Nofre et al (U.S. Patent No. 5,480,668) would inherently produce crystalline N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L-α-aspartyl]-L-phenylalanine 1-methyl ester, which exhibits X-ray diffraction peaks at 2θ diffraction angles of 5.55° , 12.25° , 18.5° , 21.1° and 22.45° with CuKα rays. This assertion is *not* correct.

Even if a general reductive alkylation method (column 7, lines 24-51) for synthesizing the compounds shown in Table 1 (column 8), and recrystallization of the compound from an ethanol/water mixture or acetonitrile (column 7, lines 48-49) are applied to the compound of the present invention, the aforementioned crystalline compound cannot be obtained.

In the method of Nofre et al, "[t]he gummy precipitate formed is filtered off, dried under vacuum and recrystalized from an ethanol/water mixture (1/1) or from acetonitrile." However, the gummy product obtained during synthesis of the claimed crystalline compound cannot be recrystalized if the lipid-soluble impurities are attempted to be removed therefrom as described in Nofre et al for the following reasons:

The purification method of Nofre et al (column 7, lines 45-49) can be briefly summarized as follows: the solvent (methanol) is removed from the reaction mixture by vacuum concentration, 1N aqueous solution of hydrochloric acid is added until the pH is approximately neutral, the gummy precipitate formed is filtered from aqueous solution, the gummy precipitate is vacuum dried, and then recrystallized from an ethanol/water mixture (1/1) or from acetonitrile. During the above procedure, the reaction reagents and byproducts

can be removed only during washing with 1N HCl and recrystallization. In the case of compound 6, (N-[N-(3,3-dimethylbutyl)-L-alpha-aspartyl]-L-phenylalanine 1-methyl ester), in view of the low boiling point of the starting material (3,3-dimethylbutylaldehyde), unreacted aldehyde might be removed during vacuum concentration.

However, in case of compound 18 (the amorphous form of the compound of the present invention), a starting material such as 4-hydroxy-3-methoxyphenylpropionealdehyde may be used. This is problematic in that it is difficult to remove the unreacted aldehyde and by-products derived therefrom. In using the process disclosed in Nofre et al, relatively water-soluble reagents and by-products may be removed from the reaction product; however, lipid-soluble impurities appeared to be extremely difficult to remove from the reaction product. In this condition, the inventive compound cannot be recrystallized due to the residual presence of lipid-soluble impurities.

To this end, the process disclosed by Nofre et al was attempted, but the product (compound 6) could not be obtained as a crystal. Therefore, a further purification step (i.e., column chromatography) had to be added, which permitted recrystallization of the thus obtained purified product from a methanol/water. This same problem would exist for recrystallization of any of the compounds listed in Table 1 of Nofre et al, including compound 18.

Therefore, to solve the problems above (i.e., to remove lipid-soluble impurities from the reaction mixture), the present invention was completed. In example 1 of the present specification, the lipid-soluble impurities are removed by 50 ml ethyl acetate and 5 ml methanol extraction. In example 2, the residual aspartame is removed at first by adding 20 ml ethyl acetate and 2 ml of methanol and then the product is recovered by water extraction to

remove the lipid-soluble impurities. Only after additional purification procedures to those disclosed by Nofre e al were added could N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L-α-asparlyl]-L-phenylalanine 1-methyl ester be obtained as a crystal. More specifically, based on the process disclosed by Nofre et al, it is not possible to obtain crystalline N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L-α-asparlyl]-L-phenylalanine 1-methyl ester, which exhibits X-ray diffraction peaks at 2θ diffraction angles of 5.55° , 12.25° , 18.5° , 21.1° and 22.45° with CuKα rays.

Claude et al (U.S. Patent No. 5,510,508) is also cited by the Examiner, but this reference does not compensate for the aforementioned shortcoming in the disclosure of Nofre et al.

7. I declare further that all statements made of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of this application or any patent issuing thereon.

8. Further Declarant saith not.

Yusuke Amino

Name: Yusuke Amino, Ph. D.

November 30, 2004

Date